

### SPECIFIC AIMS

The Symposium on CENTRAL NEURAL MECHANISMS PRODUCING PERIODIC RESPIRATORY MOVEMENTS has three aims:

1) to bring together researchers with diverse approaches to the study of different aspects of central neural production of respiratory movements in mammals.

2) to define and focus on the important questions that need to be answered in order to understand both normal and pathological states of respiratory movement production. This is a very timely issue (See Timeliness Below).

3) to present and critically discuss research results, particularly in reference to the issues defined in 2). In order to focus this meeting, we will concentrate on those issues related to the determination of the biophysical properties of and the interactions between neurons underlying production of periodic respiratory movements.

### OBJECTIVES

Periodic respiratory movements generated by the diaphragm, intercostal, abdominal and laryngeal musculature are necessary for ventilation in mammals. Respiratory movements must be maintained and regulated throughout life. Since the diaphragm, intercostal, abdominal and laryngeal musculature are skeletal muscles, the movements they generate are entirely under the control of the central nervous system. Diseases such as Sleep Apnea, Sudden Infant Death Syndrome, Cheyne-Stokes respiration, Ondine's Curse Syndrome, may involve central nervous system dysfunction related to the production of periodic respiratory movements.

The goals of the proposed symposium are to explicitly define the questions that need to be answered in order to understand the central neural production of respiratory movements and to critically discuss current research aimed at this understanding. The need for a meeting having these goals is important, as well as timely, for the following reasons.

1) As with any complex homeostatic system under nervous control, researchers tend to study either input-output relationships, e.g. the effect of carbon dioxide on ventilation, treating central neural processing as a black box [e.g.1,7,15], or they study some isolated neural pathway, e.g. interactions between neurons in the region of the ventrolateral nucleus of the tractus solitarius, often in a reduced preparation, without particular interest or association with integrative system function [e.g.3,9,13]. This partitioning of research, while an important first step, can lead to oversimplification and serious errors when trying to understand the functioning of the normal, intact system. We believe that researchers studying central neural interactions must constantly evaluate their work in terms of the modus operandi of the system, i.e. the production of homeostatically regulated movement of respiratory musculature. In order to accomplish this goal, we plan to devote the initial part of the meeting to a series of plenary lectures by experts on respiratory movements and respiratory related sensory reception, including chemo- and mechano- reception. Presentations by these individuals will be focused upon defining the important issues that must provide the framework for all neurophysiological studies.

2) It will be important to establish what we really do and do not know about the central production of respiratory movements. For example, an important issue concerns the distinction between those neural structures lying in the final pathway for movement production and those actually producing respiratory rhythm.

Investigators have recorded and characterized respiratory related neural

activity from a variety of structures in the central nervous system. Whether in fact any or all of these structures have importance in the generation of respiratory rhythm and/or the production of respiratory movements is not at all clear. Since essentially normal periodic respiratory activity persists in phrenic and recurrent laryngeal nerves in decerebrate, decerebellate cats, dogs and monkeys, it is generally accepted that the minimal neural structures required for automatic respiratory movements are in the brainstem and spinal cord. Moreover, since spinomedullary transection abolishes periodic activity of the phrenic nerve (motoneurons in the cervical spinal cord) without altering the periodic respiratory related outflow in recurrent laryngeal nerve (motoneurons in the medulla) [4,16], it indicates that the mechanisms generating respiratory rhythm are within the brainstem. Within the brainstem, neurons with spike activity phase locked to respiratory outflow are concentrated in, but not strictly restricted to, three major regions: the ventrolateral nucleus of the tractus solitarius in dorsomedial medulla, the nucleus retrogambigialis in ventrolateral medulla and nucleus parabrachialis medialis in the dorsolateral rostral pons [at least in vagotomized animals].

It is compelling to hypothesize that respiratory rhythm is generated by a subset of these neurons. Indeed most research on brainstem mechanisms for respiratory pattern generation takes this as axiomatic, since it focuses on studying the biophysical membrane [e.g. 17,18] or network interactions [e.g. 2,3,9,11,13,20] of these neurons without explicitly demonstrating their role in rhythmogenesis. It must be emphasized that the location within the brainstem of the respiratory rhythmogenic mechanisms is unknown. This raises two fundamental issues:

a) without explicitly demonstrating the role of a given subset of analyzed neurons in respiratory pattern generation, is it possible to evaluate the significance of experimentally determined neuronal properties in terms of pattern generation?;

b) are current experimental protocols appropriate for locating and determining the operating features of the brainstem respiratory oscillator?

It is issues such as these which need to be addressed, in order that current experimental protocols can be reevaluated and new experiments can be designed to answer questions of fundamental importance.

3) In light of the above issues, it would be important to present and critically discuss current research results and suggest appropriate directions for research on the important physiological problem of the central generation and control of respiratory pattern.

#### TIMELINESS

We strongly believe that the issues discussed above are timely and a meeting organized around the proposed themes would allow a more unified and coherent effort among different laboratories directed towards the important problem of central generation of respiratory movements. As previously mentioned, we feel that this important field is suffering from the lack of a clear definition of the fundamental issues and problems, as well as from confusion between broadbased theoretical evaluations [e.g.5,12,19] and the "mundane" facts of neurophysiology[see review ref. 6]. We believe that in the present atmosphere the most important experiments will not be performed. A frank, open discussion at this time amongst the researchers in this field, to evaluate present knowledge and set goals for the future, is sorely needed.

#### PREVIOUS MEETINGS

A meeting focused the central nervous mechanisms in the production of periodic respiratory movements has not been held previously. It is unlikely that another meeting of this kind will be organized at any time in the near future on this or any related theme. The American Physiological Society or the Society for Neuroscience do not organize symposia of this sort, preferring to invite a limited number of investigators to present "didactic" lectures, e.g. the FASEB Symposium on Central Respiratory Rhythmicity [Anaheim, 1980, Fed. Proc. in press] had 5 short didactic presentations directed to a "general" audience. Although it is possible that a symposium on a related subject will be planned for the 1983 IUPS meeting in Australia, it is unlikely that a significant contingent of American researchers will be able to participate given the current trends in transportation costs.

In prior years there have been several international meetings attended by individuals interested in the neural control of breathing. Unfortunately, these meetings have either been diffuse, or focused upon other issues. For example, the meetings in Amiens, France (1976) [8], Paris (1977) [14], and Stockholm (1978) [10] were very general meetings, having broadly defined themes and limited time for formal (and informal) discussion in an open forum. Thus, these gatherings resulted in poor interactions. In 1980 a meeting was held in Heidelberg, Germany on "The Role of the Nucleii Tractus Solitarius in the Central Regulation of the Respiratory and Cardiovascular Systems." While this meeting was well focused, and provided for interactions between respiratory and cardiovascular neurophysiologists, it addressed a significantly different theme from the one we are proposing. An outcome of the informal discussions among the respiratory neurophysiologists at that meeting was the realization of the need for a meeting organized around the theme proposed in this application. As a result, Drs J.L. Feldman and A.J. Berger were asked to organize a workshop dealing with the central production of respiratory movements.

#### SELECTION OF SPEAKERS

The major participants will be investigators of recognized stature in this field based on their contributions. The tentative list of topics which follows is an indication of our intentions in this regard. However, since it is possible that less well established investigators or others who escape the notice of the organizing committee will have important work to present, the meeting will be publicized widely and a request for abstracts sent out. The organizing committee will review these abstracts and formalize our decisions on speakers for the general presentations. We expect 35-50 invited speakers with total participation not to exceed 100. We will restrict attendance and support to individuals who will clearly contribute to the theme of this symposium. (See TENTATIVE LIST OF TOPICS AND SPEAKERS).

In order to insure the circulation of the proceedings of this meeting, particularly the discussions relating to the themes, a book will be published. Negotiations are currently under way with several publishers.

#### DATE AND SITE OF MEETING

We propose to hold the meeting at the Harrison Conference Center, Lake Bluff, Illinois. This center is located north of the Medical School of Northwestern University and is well equipped to handle meetings of the kind we are proposing. There is on site housing and full facilities including excellent meeting facilities for 100 individuals. Projected costs for room, board and meeting facilities are \$100/day/individual.

We believe that it will take four full meeting days to adequately cover

the topics we are proposing. We are planning to hold this meeting April 14-18, 1982. This is immediately before the spring FASEB meetings and would allow the participants of both meetings to go directly from this symposium to FASEB (in New Orleans), reducing their travel costs. This scheduling would also permit foreign researchers, who would not otherwise be able, to attend FASEB.

#### PROGRAM

All of the investigators we have spoken to about this meeting have expressed a strong preference for the program to be organized as an intense workshop. Each meeting day will start with breakfast for all of the participants, followed by a "formal" program of presentation and discussion from 9 A.M. to 7 P.M., with a break for lunch, of course. This will be followed by dinner for all of the participants. After dinner, a lounge will be available for extended informal discussion. Due to the relative isolation of the ALLEN CENTER from any sort of night life, we expect that the informal evening sessions will be well attended.